REMARKS

The Office Action of March 3, 2009, has been carefully studied. Claims 1, 4, 5, 9-17 and 19-23 currently appear in this application. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicant respectfully requests favorable reconsideration and formal allowance of the claims.

Claim Amendments

The claims have been amended to change "physiologically active protein" to --genetically recombinant protein--. Support for these amendments can be found in the specification as filed at page 6, lines 27-28. The concentration has been amended to "ionic concentration." The pH range has been amended to "from 4.0 to the isoelectric point of the protein."

Title

The title has been changed to "METHOD FOR REMOVING DNA CONTAMINANTS FROM A PROTEIN-CONTAINING SAMPLE."

Abstract

The abstract is objected to.

Submitted herewith is a new abstract on a separate sheet of paper.

Claim Objections

Claim 9 is objected to because "treatment of removal" should be --treatment for removal--.

The present amendment makes this change.

Claims 18 and 20 are objected to for reciting non-elected subject matter.

Claim 18 has been rewritten as new claim 23 and claim 20 has been amended to depend from claim 23. Since claim 23 depends from claim 1, which was considered to be drawn to elected subject matter, it is not understood why claims 18 and 20 would be considered to be drawn to non-elected subject mater, particularly since claims 18 and 20 were originally included in the claims elected.

Double Patenting

Claims 1, 4, 5, 9, 10 and 17-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 5, 6, 8 and 13 of US Patent 7,332,289.

Submitted herewith is a terminal disclaimer signed by the undersigned which should be sufficient to overcome this double patenting rejection.

Claims 1, 4, 5, 9, 10 and 17-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 5, 7, 8 and 14 of U.S. Application No. 12/018,688.

Submitted herewith is a terminal disclaimer signed by the undersigned which should be sufficient to overcome this double patenting rejection.

Rejections under 35 U.S.C. 112

Claims 1, 4, 5, 9, 10 and 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention

This rejection is respectfully traversed.

The claims have been amended to recite "genetically recombinant protein." Support for this can be found in the specification as filed at page 6, line 27.

"Concentration" has been changed to --ionic concentration--. As can readily be seen from the specification, one of the important features of the claimed method is to form a low conductivity solution, and it is well known that the conductivity of a solution depends upon its ionic strength, that is, the ionic concentration, of the solution. Thus, it is respectfully submitted, from the specification, particularly from the working examples, it can be clearly understood that "concentration" as used in the herein claimed method means ionic concentration in the solution.

With respect to pH n the claims, it is meant that the lower limit of pH is 4.0 and the upper limit of the pH is the isoelectric point of the protein. Thus, as stated above, the pH range is recited as "pH from 4.0 to the isoelectric point" in order clearly to describe the meaning.

Claims 1, 4, 5, 9, 10 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner alleges that the specification teaches no methods for removing DNA contaminants from a sample by forming particles of DNA, wherein the protein remains active after the removal of DNA contaminants.

This rejection is respectfully traversed.

The specification specifically states at page 13, lines 3-21, that the method involves removing impurities from a physiologically active protein by forming a solution containing the physiologically active protein at a pH equal to or lower than the isoelectric point of the protein, and removing particles formed in the solution. Examples of impurities that form such particles are DNA contaminants, viruses, Protein A, endotoxins, HOC (host cell-derived proteins), etc. "DNA contaminants" is defined as DNA molecules present in a physiologically active protein-containing sample.

Specific examples of purifications are shown in Example 2, purification of humanized anti-PTHrP antibody (removal of residual DNA in the eluate) and Example 3, purification of humanized anti-HM1.24 antigen monoclonal antibody (removal of residual DNA).

It is not understood why the Examiner alleges that there is no written description for removing DNA contaminants from a sample when two specific examples describe such removal.

Art Rejections

Claims 1, 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Oxenburgh et al., Nature **207**:1416-1417, 1965.

This rejection is respectfully traversed.

The claims have been amended to recite that the method depends on adjusting the pH from 4.0 to the isoelectric point of the protein to be purified. There is nothing in Oxenburgh that even mentions the isoelectric point of the protein. Additionally, Oxenburgh uses streptomycin to precipitate nucleic acids, which is not needed in the herein claimed method.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Oxenburgh in view of Kipriyanov et al., *Molecular Biotechnology* **12**:173-201, 1999.

This rejection is respectfully traversed.

The presently claimed method is based upon a new finding that DNA contaminants can be separated as particles form an aqueous solution of a protein-containing sample when the pH of the solution is adjusted to from 4.0 to the isoelectric point of the protein under low conductivity conditions, namely, an ionic concentration of 100 mM or less. This particle formation, remarkably, can be visually observed.

Therefore, satisfying each limitation the claimed method is critical to the claimed method in order to remove DNA contaminants effectively from a sample without the need for a complicated process such as a chromatographic treatment. Moreover, the protein is now recited as a "genetically recombinant protein", which was not even contemplated by Oxenburgh in 1965.

There is nothing in either Oxenburgh or Kipriyanov, taken alone or together, that even suggests that DNA contaminants dissolved in solution can be insolubilized and removed under conditions of specific pH and ionic concentration ranges.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Oxenburxch in view of Somack et al., 1999.

This rejection is respectfully traversed.

Even though Somack discloses that precipitated DNA can be removed by filtration, Oxenburgh does not disclose how to form this DNA precipitate. There is nothing in Overmuch that even suggests adjusting the pH

and the isoelectric point of a solution in order to precipitate DNA. Moreover, Oxenburgh did not even contemplate solutions of recombinant proteins.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Oxenburgh in view of what was well known in the art,.

This rejection is respectfully traversed.

Whether or not pH 7.0 and 7.6 are functionally equivalent depends upon the function being considered. Therefore, one skilled in the art, reading Oxenburgh, would have no way of knowing that a pH of 7.5 to 13 would be functionally equivalent to a pH of 7.0 in precipitating DNA, particularly because the ionic concentration of the solution must also be taken into account.

Claims 9 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oxenburgh and Kipriyanov in view of Harlow et al., 1988 as evidenced by Fahrner et al., 1999.

This rejection is respectfully traversed.

There is absolutely nothing in any of the cited references that even suggests considering the isoelectric point of the solution when precipitating DNA contaminants. It is critical to the herein claimed method that both the pH and the ionic concentration be adjusted in order to precipitate DNA contaminates from a solution. This is neither shown nor suggested by any of the cited references, either alone or in combination.

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Oxenburgh in view of Kipriyanov, Harlow and Fahrner in view of Sigma, Inc.

This rejection is respectfully traversed.

The fact that Sigma teaches an aqueous solution of 500 mM Tris at pH 3.5-5.0 does not suggest that this solution can be used to adjust the antibody-containing solution of Harlow. The critical element missing in all of these references is that the pH **and the ionic concentration (isoelectric point) of the solution must be adjusted**. There is no suggestion in any of these references that would lead one skilled in the art to use the Sigma solution in a protein-containing solution, particularly when the pH of the solution must be adjusted to be not greater than the isoelectric point of the solution.

Claims 1, 4, 5, 9, 10, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lydersen et al., 1994 in view of Harlow as evidenced by Farer.

This rejection is respectfully traversed. The Examiner has admitted that Lydersen does not teach using the method wherein the salt concentration is less than 100 mM or less. There is nothing in the combination of Lydersen, Harlow and Fahrner that even suggests that DNA contaminants can be precipitated and thus removed from a protein-containing solution by controlling **both** the pH and the ionic concentration.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Lydersen, Harlow and Fahrner in view of Somack.

This rejection is respectfully traversed.

The fact that Somack removed DNA precipitate by filtration adds nothing to Lydersen, Harlow and Fahrner, taken alone or in combination. None of these references suggests that DNA contaminants can be precipitated form a protein-containing solution by controlling pH and isoelectric point along with the ionic concentration.

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Lydersen, Harlow and Fahrner in view of Sigma.

This rejection is respectfully traversed.

The fact that Sigma teaches an aqueous solution of 500 mM Tris at pH 3.5-5.0 adds nothing to the cited references. There is no suggestion for using the Sigma solution in any of the methods of the cited references. Moreover, there is no teaching or suggestion for controlling the pH/isoelectric point and ionic concentration of the solution to be treated.

As stated above, the presently claimed method is based upon an unexpected finding that DNA contaminants dissolved in a solution can be insolubilized under conditions of specific pH and ionic concentration ranges.

However, none of the cited references nor any common knowledge available at the time of the filing of the present application teaches or suggests that there is any relationship between an ionic concentration and pH range of a protein-containing solution and formation of particles of DNA contaminants.

Accordingly, it is respectfully submitted that controlling the pH and ionic concentration of a protein-containing solution to precipitate and remove DNA from a solution would not have been appreciated by one skilled in the art reading the cited references.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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